J Cancer Res Clin Oncol (2001) 127: 48–54

ORIGINAL PAPER

R. Kath · K. Blumenstengel · H. J. Fricke · K. Höffken

Bendamustine monotherapy in advanced and refractory chronic lymphocytic leukemia

Received: 25 May 2000 / Accepted: 30 June 2000

Abstract Bendamustine, an alkylating agent without cross-resistance to cyclophosphamide is active in a variety of lymphoproliferative and other malignancies. In an open phase-II study we treated 23 patients with a median age of 62 years at study entry (43–86 years) with advanced, refractory or relapsed (Rai stage III $n = 9$, Rai stage IV $n = 14$) chronic lymphocytic leukemia (CLL) with bendamustine. At study entry, only 13 patients were chemotherapy-naive. The treatment schedule with bendamustine was as follows: for patients up to 70 years 60 mg/m^2 for 5 days, for patients over 70 years 50 mg/m^2 for 5 days, repetition at day 29. Remission criteria were used according to Cheson et al. (1996). All patients were evaluable for toxicity and 20 for response. An objective remission was achieved in 15/20 patients (75%), including six patients with complete remission (CR). Three of the complete responders had no chemotherapy prior to bendamustine. No change (NC) occurred in 5/20 patients (25%). Median overall survival after bendamustine treatment is 13.6 months (1–46 months) and 16.6. months (1–46 months) in patients responding to bendamustine. In total, 74 courses of bendamustine were applied. Therapy-related anemia and thrombocytopenia were rare. However, WHO grade III/IV leukocytopenia occurred in 38/74 cycles (51%), resulting in treatment-related mortality in 3/23 patients (13%). These patients were severely immunocompromised due to pretreatment or the underlying disease. As a corollary of the study, a general prophylactic antibiotic treatment (trimethoprim/sulfamerazine) was instituted. A general feature was the decline of the CD4/CD8 ratio: mean before therapy: 1.36; after two courses: 0.98; after four courses: 0.6, as documented in all patients who received at least two courses of bendamustine ($n = 12$). All evaluable patients showed a decline in the CD4/8 ratio. However, this decline was not clearly related to an increased risk of infectious episodes. We observed mainly cutaneous allergic reactions (three WHO grade I; one WHO grade II) leading to a cessation of bendamustine treatment in 4/23 patients (18%). Bendamustine is highly effective in advanced or refractory CLL. In multiple pretreated or otherwise severely immunocompromised patients bendamustine might lead to additional immunosuppression with subsequent infectious complications.

Key words Bendamustine · Chronic lymphocytic leukemia · CD4/8

R. Kath · K. Blumenstengel · H. J. Fricke · K. Höffken
Klinik und Poliklinik für Innere Medizin II der Friedrich Schiller Universität Jena, Erlanger Allee 101, 07740 Jena, Germany
e-mail: Roland.Kath@polkim.med.uni-jena.de

R. Kath (✉)
Medizinische Klinik I, Philippsstift, Kathol. Krankenhaus Essen-Borbeck, Hülsmannstrasse 17,
45355 Essen, Germany

Introduction

The cornerstone of treatment in advanced CLL remains alkylators. However, after progression to chlorambucil or cyclophosphamide, there are only few active treatment alternatives that correspond to the mainly elderly patients in a reduced general condition. The alkylator bendamustine, a nitrogen mustard derivative, with anticipated antimetabolite activity, has shown to be highly effective in lymphoproliferative diseases including CLL with no cross-resistance to cyclophosphamide. It has been studied in experimental animal studies (Jungstand et al. 1971; Kramaczyk and Jungstand 1971; Ozegowski and Krebs 1971; Strumberg et al. 1996) and clinical investigations focusing on malignant lymphomas (Anger et al. 1967a, 1975; Blumenstengel et al. 1997, 1998; Bremer and Roth 1996; Heider et al. 1997; Herold et al. 1987; Junghanss et al. 1996; Kahl et al. 1997; Ruffert et al. 1989, 1998; Poenisch et al. 1999), breast cancer (Schmidt et al. 1999; Brockmann et al. 1991; Meyer et al. 1998; Ruffert et al. 1998; Höffken et al. 1998), and small cell and non-small-cell lung cancer (Reck et al. 1998; Heider et al. 1999). In multiple myeloma, bendamustine has shown promising results in combination

with vincristine and prednisolone and versus MP (Blumenstengel et al. 1998; Heider et al. 1997; Bremer and Roth 1996; Poenisch et al. 1999). The same holds true for other low- and high-grade non-Hodgkin's and Hodgkin's lymphomas (Bremer 1994; Ruffert et al. 1998b; Heider et al. 2000).

Side-effects of the drug are relatively mild with myelosuppression as the dose-limiting toxicity (Anger 1967a; Bremer and Roth 1996; Matthias et al. 1995; Reck et al. 1998; Höffken et al. 1998). There is no consistent alopecia associated with bendamustine. Allergies have been reported but no prophylactic application of steroids is recommended. The maximal tolerated dose (MTD) has been defined at 215 mg/m^2 as a 1-day schedule and 70 mg m^2 per day as a 4-day schedule. However, bendamustine is usually applied at a dose of 100–120 mg m^2 per day, day 1 and 2. Recently, a phase-1 study, investigating a day-1 and 8 schedule, obtained an MTD of 160 mg/m^2 (Schöffski et al. 2000).

So far, the activity of bendamustine in CLL has not been thoroughly investigated. In a randomized study 70 CLL patients received bendamustine or cyclophosphamide monotherapy as first chemotherapy (Anger 1975). In 39 patients, bendamustine induced 82% remissions, whereas a significantly lower remission rate of 32% was obtained in 31 patients with cyclophosphamide. Six patients with CLL resistant to cyclophosphamide and chlorambucil, all achieving a remission after salvage therapy with bendamustine, were reported by Bremer (Bremer 1994). We performed a single-center phase-II study to determine the activity and toxicity of a monochemotherapy with bendamustine in immunocompromised patients with advanced CLL.

Patients and methods

Eligibility criteria

Patients were required to have a B-cell type CLL of Rai stage III or IV. Immunophenotyping was performed to confirm the diagnosis. Patients were required to have progressive, refractory or relapsed disease and had to be free of prior chemotherapy for 4 weeks or more. All patients were older than 18 years. No upper age limit was specified. However, a performance status ≤2 or a life expectancy of ≥3 months were required as well as absence of active infection. Exclusion criteria were inadequate hepatic, renal or cardiac dysfunction, or peripheral blood cytopenia if not clearly related to bone marrow infiltration of CLL. The extent of disease was determined by standardized staging evaluations, including physical examination, bone marrow aspiration, and trephine biopsy. CT scanning of the chest, abdomen, and pelvis were performed.

Treatment protocol

Therapy consisted of a 30-minute i.v. infusion of bendamustine, given on days 1–5 at a dose of 60 mg/m^2 for patients up to 70 years old and 50 mg/m^2 for patients 70 years and older, with repetition at day 29. Treatment was stopped at CR or best response, PD, unacceptable toxicity or at poor performance status. At the beginning of the study, no routine antimicrobial prophylaxis was given. However, due to repeatedly occurring septicemia, a routine prophylactic supportive treatment with trimethoprim/sulfamerazine was performed in the second half of the study. No routine antiemetics or steroids were administered.

Response and toxicity criteria

All responses and toxicities were reviewed by one of us using response criteria recommended by the National Cancer Institute Working Group (Cheson et al. 1996) and WHO toxicity criteria (Miller et al. 1981). Peripheral lymph node enlargements, splenoand hepatomegaly were documented after each bendamustine cycle. Sites of disease not assessable by clinical examination were monitored by chest X-ray, CT scan, and/or bone marrow aspiration after two cycles as well as at completion of bendamustine therapy. Duration of remission was assessed through clinical and radiological (where appropriate) examinations as well as blood cell counts at three-month intervals until relapse. Full blood counts including differential were done weekly during treatment with bendamustine. The CD4/8 ratio was monitored before and after every second course of bendamustine using Simulset software and antibodies from Beckton Dickinson.

Results

We report on 23 patients with previously treated ($n = 10$) or untreated ($n = 13$) CLL receiving mono-chemotherapy with bendamustine. All patients ($n = 23$) were evaluated for toxicity and if possible for response ($n = 20$), time to treatment failure ($n = 20$), and survival ($n = 23$). Patient characteristics are illustrated in Tables 1 and 2. Prior treatments consisted mainly of chlorambucil/prednisolone with or without other treatment protocols including cyclophosphamide, vincristine, bleomycin, adriamycin, fludarabine, estramustine, and 2-chlorodeoxyadenosin as indicated in detail in Table 1. A total of 74 courses of bendamustine were administered (medium of two courses per patient, ranging from 1–8 courses). Salvage treatment after bendamustine was heterogeneous, described in Table 1. The study started in May 1995. The last follow-up was performed in February 2000. The median age at the start of bendamustine treatment was 62 years (43–86 years), and 59 years (41–86 years), calculated from the time of diagnosis.

Responses

A complete or partial remission (CR/PR) was achieved in 15/20 patients (75%), including six patients with CR (Table 3). Three of the complete responders progressed after prior chemotherapy. No change (NC) occurred in 5/20 patients (25%). No patient progressed while on bendamustine treatment. Median survival calculated from the start of bendamustine treatment is 13.6 months (1–46 months) (Fig. 1). Patients achieving a CR ($n = 6$) had a longer survival than patients not achieving CR (Fig. 2). However, due to small numbers, this difference is not statistically (Wilcoxon test) significant ($P = 0.0527$).

Toxicity

There was no consistent alopecia. Therapy-related anemia, thrombocytopenia and phlebitis were rare

Table 1 Detailed characteristics and clinical course of CLL patients treated with bendamustine (*Adr* Adriamycin, *Benda* bendamustine, *Bleo* bleomycin, *Chlor* chlorambucil, *CR* complete remission, *Cyclo* cyclophosphamide, *Flud* fludarabine, *Estram* estramustine, *F* female, *Ida* idarubicin, *IFN* interferon, *M* male, *maint* maintenance therapy, *NC* no change, *n.e.* not evaluable, *PD* progressive disease, *PR* partial remission, *Pred* prednisolone, *VCR* vincristine, *2-cDA* 2-chlorodeoxyadenosine)

Patient	Age at diagnosis/ study entry (years)	Sex	Rai stage	Pretreatment (no. of different protocols)	No. of Benda cycles	Response	Clinical course	Response duration after Benda (months)	Survival since Benda (months)
1	73/76	M	IV	Chlor/VCR/Pred then VCR/Pred (2)	2	PR	Death due to cardiac ingestion	1	2
2	72/74	F	III	–	4	CR	Lasting CR without maint	29+	31+
3	41/43	F	IV	–	5	CR	Maint IFN, PD, again response to Benda	32	46+
4	44/44	F	III	–	2	PR	Allergic reaction to Bend., 2 × 2cDA achieving a lasting PR without maint	n.e.	29+
5	67/68	F	IV	Chlor/Pred then Cycl/VCR/Pred (2)	2	CR	No maint, death due to cardial ingestion	9+	11
6	66/67	F	IV	Chlor/Pred then Cycl/VCR/Pred (2)	3	NC	Severe autoimmune thrombocytopenia	–	13
7	86/86	F	III	–	2	PR	No maint, death due to cardial event	10+	11
8	62/62	F	IV	–	1	PR	Death due to cardial ingestion	2+	2
9	67/75	F	III	Chlor/Pred then Cycl/VCR/Pred than Bend/VCR/Pred then IFN (4)	1	n.e.	Death due to septicemia	–	2
10	55/55	M	IV	–	6	CR	No maint, death due to PD	12	16
11	60/60	M	IV	–	1	PR	Allergic reaction to Bend, then Chlor/Pred	n.e.	19+
12	54/54	M	IV	Flud (1)	6	CR	No maint, relapse 1xChor/Pred, 3xBend, 3xCHOP, 1xIda, 1xFlud, 2xBleo/Pred (none with response)	18	38+
13	61/61	F	III	Chlor/Pred (1)	5	PR	Maint IFN, relapse Cyclo, severe infections	4	26
14	51/51	F	III	–	2	NC	Allergic reaction to Bend	–	4+
15	48/48	M	III	–	2	PR	Allergic reaction to Bend, then Cyclo/VCR/Pred	n.e	4+
16	57/59	M	IV	Chlor/Pred then Estram then Cycl/Pred then Bleo/Adr/VCR then Flud (4)	8	NC	Control of disease than death due to PD	–	9
17	56/61	M	III	–	6	NC	Control of disease then PD, 6 × Chlor/Pred	–	20+
18	46/54	F	IV	Chlor/Pred then Cycl/VCR/Pred then IFN (3)	1	n.e.	Death due to septic pneumonia	n.e.	1
19	66/66	M	IV	–	1	n.e.	Death due to septic event, pseudomonas infection	n.e.	1
20	61/61	M	IV	–	1	PR	Allergic reaction to Bend, no further therapy due to phlebothrombosis	3+	4+
21	52/52	M	IV	Chlor/Pred (1)	4	PR	No maint, PD, than Idar, NC	5	8
22	55/56	M	IV	Chlor/Pred (1)	8	CR	No maint	4+	13+
23	59/62	M	III	2–cDA (1)	2	NC	Septicemia	–	5

Table 2 Characteristics of CLL patients treated with bendamustine

No. of patients	
Total	23
Gender	
Male	12
Female	11
Rai stage	
III	9
IV	14
No. of pretreatments	
0	12
1	5
2	3
3	2
4	1
No. of patients (at study entry) with:	
Enlargement of peripheral lymphonodes	19
Spenomegaly	21
Hepatomegaly	21
Hemolysis	3
Age (in years)	
Median	62 (at start of bendamustine)
Range	43–86
Median	59 (at diagnosis)
Range	41–86
Blood values at study entry (SI) HB (mmol/l)	
Median	6.4
Range	3.4–10.4
Leukocytes $\times 10^9$/Gpt	
Median	100
Range	5–475
Platelets $\times 10^9$/Gpt	
Median	117
Range	10–313

Table 3 Response rates of evaluable CLL patients treated with bendamustine

CR	n = 6/20 (30%)
PR	n = 9/20 (45%)
NC	n = 5/20 (25%)

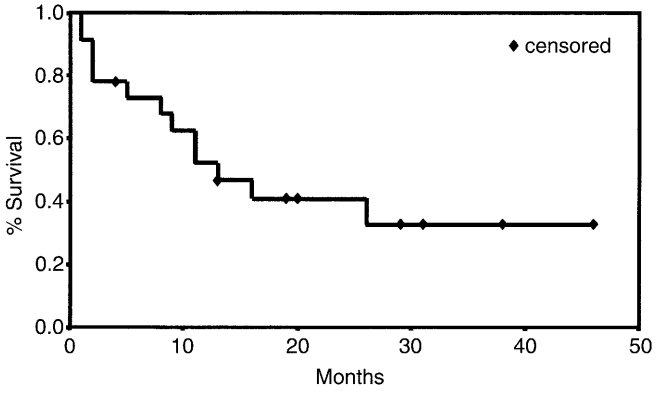

Fig. 1 Kaplan-Meier survival plots of patients with CLL treated with bendamustine calculated from the beginning of bendamustine treatment

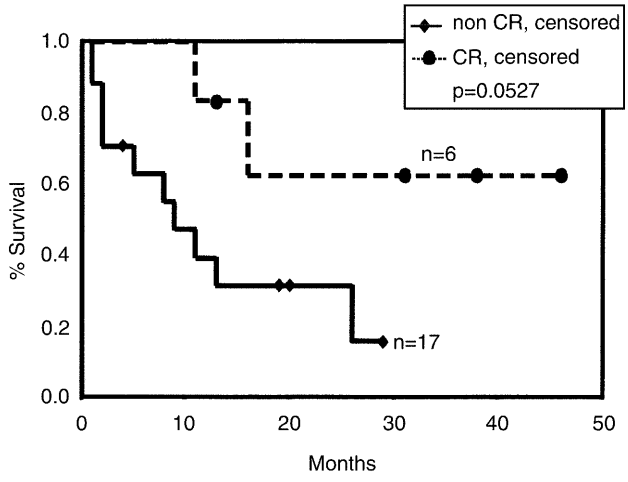

Fig. 2 Kaplan-Meier survival plots of patients with CLL treated with bendamustine calculated from the beginning of bendamustine treatment comparing patients achieving a CR ($n = 6$) with those not achieving a CR (PR $n = 9$, NC $n = 5$, not evaluable $n = 3$)

Table 4 Toxicity of CLL patients treated with bendamustine related to a total of 74 (%) evaluable courses

WHO grade	I	II	III	IV
Leukocytes	7 (9)	26 (35)	31 (41)	7 (9)
Thrombocytes	10 (13)	6 (8)	3 (4)	5 (7)
Hemoglobin	14 (19)	5 (7)	2 (3)	2 (3)
Allergy	3 (4)	1 (1)	0	0
Emesis/vomiting	10 (13)	3 (4)	0	0
Alopecia	5	0	0	0
Phlebitis	6	0	0	0

(Table 4). However, WHO grade III/IV leukocytopenia occurred in 38/74 cycles (51%), resulting in treatment-related mortality in 3/23 patients (13%). These patients (patients 9, 18, and 19, referring to Table 1) died due to septicemia in myelosuppression. Patient 9 was a 75-year-old female with an eight-year history of CLL. She was heavily pretreated with chlorambucil/prednisolone then cyclophosphamide/vincristine/prednisolone and interferon-alpha. Due to progressive disease with chronic intermittent infections she was treated with one course of bendamustine. Prior to treatment she had a CD4/8 ratio of 1. There was no acute toxicity to bendamustine. Shortly before the second planned course of bendamustine she was readmitted to the hospital because of pneumonia and severe myelosuppression (leukocytopenia and thrombocytopenia grade IV according to WHO). The differential blood count showed no granulocytes. Erythrocytes also had to be substituted. The patient died due to a long-lasting irreversible myelosuppression 2 months after bendamustine treatment, due to a septic event. The second case of treatment-related mortality was similar. In addition, patient 18, a 54-year-old female, was heavily pretreated (chlorambucil/prednisolone then cyclophosphamide/vincristine/

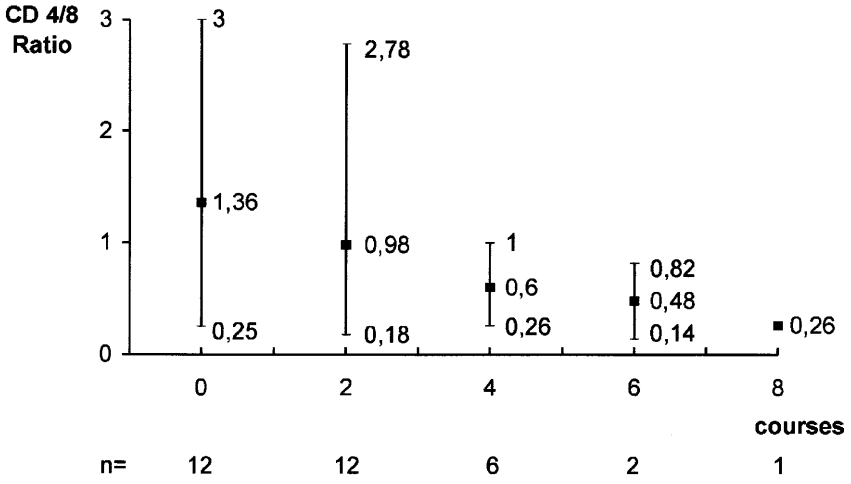

Fig. 3 Mean CD4/8 ratio of patients treated with bendamustine. Only patients (2–7, 10, 12–16 according to Table 1) were considered who received at least two courses of bendamustine ($n = 12$ before treatment, $n = 12$ after two courses, $n = 6$ after four courses, $n = 2$ after six courses, $n = 1$ after eight courses)

prednisolone and interferon-alpha). She had an eight-year history of CLL. Before treatment with bendamustine the CD4/8 ratio was 0.95. She was readmitted to the hospital 1 month after bendamustine treatment due to septic pneumonia. The differential blood count showed no granulocytes. Red blood cells and thrombocytes had to be substituted. The patient died 2 months after bendamustine treatment during a respiratory failure. In both patients (9 and 18) microbial analysis could not identify the cause of the infection. Patient 19 was a 66-year-old male with no prior chemotherapy. Before treatment with bendamustine leukocytes were 299×10^9/Gpt (98% lymphocytes). The CD 4/8 ratio was 0.75. Red blood cells were substituted due to a hemoglobin of 4.2 mmol/l. Only a few days after bendamustine treatment the patient developed a pancytopenia. Thus, supportive treatment (blood products, antibiotics, antimycotics, antiviral treatment, and G-CSF) in an intensive care unit were administered. However, the patient died 36 days after bendamustine treatment due to septic pneumonia and cardiac decompensation. Microbial analysis revealed a *Pseudomonas* infection.

A general feature was the decline of the lymphocyte CD4/CD8 ratio. All evaluable patients showed a decline in the CD4/8 ratio. The mean CD4/CD8 ratio before therapy was 1.36; after two courses 0.98; after four courses 0.6, tested in 12 patients receiving two or more cycles of bendamustine (Fig. 3). However, we could not correlate this decline to increased infectious episodes or septic events, since we only considered patients for CD 4/8 follow-up who received at least two courses of bendamustine. None of the patients who died due to septic events received two courses of bendamustine. Furthermore, in the other patients, none of those who received more than four courses (patients 2, 3, 6, 13, and 16) suffered from infectious episodes.

We observed mainly cutaneous allergic reactions in 4/23 patients (18%), easily controllable by steroids and an anti-histamine. There was one case of bronchospasm (WHO grade II), treatment was not repeated for a second course.

Discussion

Bendamustine was developed in the early 1960s as a water-soluble anticancer agent (Schnabel et al. 1967). The clinical use of bendamustine dates back to 1967 (Anger et al. 1967b, 1968). The best results were seen in patients with CLL, showing more favorable results with bendamustine than cyclophosphamide (Anger et al. 1975). Since then, the drug has been successfully applied in mono- as well as combination chemotherapy to patients with a variety of lymphoid malignancies, mainly low-grade non-Hodgkin's lymphoma including immunocytoma, CLL, multiple myeloma, and Hodgkin's lymphoma (Anger et al. 1967a, 1975; Blumenstengel et al. 1997, 1998; Bremer and Roth 1996; Heider et al. 1997, 1998, 1999; Herold et al. 1987; Junghanss et al. 1996; Kahl et al. 1997; Ruffert et al. 1989, 1998; Pönisch et al. 1999; König et al. 1999). Furthermore, it has only recently been shown that bendamustine is able to induce apoptosis in B-cell CLL alone and in combination with fludarabine in vitro (Schwaenen et al. 1999). Only few bendamustine data are dedicated to high-grade non-Hodgkin's lymphoma (Bremer and Roth 1996; Kahl et al. 1998). Also, breast cancer has been recognized as a target for therapeutic intervention with bendamustine (Schmidt et al. 1999; Brockmann et al. 1991; Meyer et al. 1998; Ruffert et al. 1998; Höffken et al. 1998). Activity was found in vitro in anthracycline-resistant breast cancer cell lines (Strumberg et al. 1996). In advanced CLL we observed a high response rate after bendamustine treatment, with a trend indicating that patients who achieve a CR might have a survival benefit. Of course, due to selection bias, this question can only be answered in a randomized study. Except for leukocytopenia, toxicity was mild. However, we observed three treatment-related deaths associated with septic events in heavily pretreated or immunocompromised patients. Thus, CLL patients under bendamustine treatment should receive a careful monitoring of blood counts and a prophylactic antibiotic treatment. In our

experience, these patients are especially susceptible to pneumonic events. Since prophylactically treating patients with oral antibiotics we have not observed any treatment-related mortality. The immune-suppressive feature of bendamustine has also been recognized by other groups. Thus, bendamustine has even been used as an immunosuppressive for treating patients with refractory autoimmune thrombocytopenic purpura (Schadeck-Gressele et al. 1998). Using flow-cytometry techniques we observed a decline of the CD4/8 ratio as a general feature. However, since there was no clear correlation between the reduction of CD4 lymphocytes and increased risk of infections under bendamustine treatment, it is not yet possible to answer the question whether a routine screening of CD4/8 in CLL under bendamustine treatment is warranted. Our incidence of mild allergies (three WHO grade I and one WHO grade, over a total of 74 courses) compares to an incidence of four allergic reactions in 43 patients (NCI grade 1 and 2) reported by Heider et al. (1998).

In conclusion, bendamustine is highly active in advanced or refractory CLL. In multiple pretreated or otherwise severe immunocompromised patients, bendamustine might lead to additional immunosuppression with subsequent infectious complications. Thus, careful patient selection should be considered. Monitoring the CD4/8 ratio was not helpful in identifying patients who developed infectious complications.

Acknowledgements We are indebted to Prof. Dr. K. H. Merkle (Ribosepharm, Munich, Germany), who contributed substantially to data analysis.

References

Anger G, Hesse P, Köhler P, Baufeld H (1967a) Erste klinische Erfahrungen mit einem neuen Zytostatikum. Dtsch Gesundheitswes 22: 1079–1084

Anger G, Hesse P, Köhler P, Baufeld H (1967b) Klinischer Erfahrungsbericht über die Anwendung des neuen Zytostatikums 3393. Z Inn Med 23: 242–247

Anger G, Hesse P, Köhler P, Baufeld H (1968) Klinischer Erfahrungsbericht über die Anwendung des neuen Zytostatikums 3393. Z Inn Med 23: 242–247

Anger G, Fink R, Fleischer J, Hesse P, Krug K, Raderecht C, Rieche K, Seibert L, Wutke K (1975) Vergleichsuntersuchungen zwischen Cytostasan und Cyclophosphamid bei der chronischen Lymphadenose, dem Plasmozytom, der Lymphogranulomatose und dem Bronchialkarzinom. Dtsch Gesundheitswes 30: 1280–1285

Blumenstengel K, Schmalenberg H, Fricke HJ, Kath R, Höffken K (1997) Bendamustine monotherapy in advanced and refractory chronic lymphocytic leukemia (CLL) (abstract). Onkologie 20 [Supp 1]: 549

Blumenstengel K, Ruffert K, Fricke HJ, Kath R, Höffken K (1998) Bendamustine vs. Melphalan in the primary treatment of multiple myeloma (MM). A randomized prospective study. J Cancer Res Clin Oncol 124 [Suppl]: R68

Bremer K (1994) Bendamustin –a promising alkylating agent noncross-resistant to other alkylators in low-grade non-Hodkgin's-lymphomas. Onkologie 17 [Supp 2]: Abstr 64, 16

Bremer K, Roth W (1996) Bendamustine, a low toxic nitrogen mustard derivative with high efficacy in malignant lymphomas. Tumordiagn Ther 17: 1–6

Brockmann B, Geschke E, Schmidt UM, Ebeling K (1991) Therapieergebnisse und toxische Nebenwirkungen der Kombination CytostasanR, Adriamycin und Vincristin als "second-line Therapie" beim metastasierten Mammakarzinom. Geburtsh u Frauenheilk 51: 1–4

Cheson BD, Benett JM, Grever M, Kay N, Keating J, O'Brian S, Kanti RR (1996) National Cancer Institute – sponsered working group guidelines for chronic lymphocytic leukemia: revised guidelines for diagnosis and treatment. Blood 87: 4990–4997

Heider A, Kress M, Niederle N (1997) Zur Rezidivtherapie mit Bendamustin bei Patienten mit Non-Hodgkin-Lymphomen von niedrigem Malignitätsgrad und Plasmozytomen. Tumordiagn Ther 18: 71–75

Heider A, Kress M, Niederle N (1998) Relapse therapy with bendamustine in patients with low-grade non-Hodgkin's lymphoma (NHL): efficacy and toxcity. Blood 92: 236b (abstract 4014)

Heider A, Köster W, Grote-Kiehn J, Bremer K, Wilke H (1999) Bendamustine in untreated small cell lung cancer (SCLC): efficacy and toxicity. Europ J Cancer 35: 254 (abstract 1009)

Heider A, Malyga C, Niederle N (2000) Efficacy and toxicity of bendamustin in patients relapsed low-grade non-Hodgkin's lymphoma (NHL). 24th National Cancer Congress of the German Cancer Society Berlin, 20–23 March 2000. J Cancer Res Clin Oncol 126 [Suppl]: R32 (abstract S02225–3)

Herold M, Anger G, Höche D, Kästner R (1987) Vorläufige Ergebnisse einer zyklisch-alternierenden Chemotherapie (CVPP/DBCy) bei fortgeschrittenem Morbus Hodgkin. Med Klin 82: 345–349

Höche D, Wutke K, Anger G (1984) Vergleichende Untersuchung zur Wirksamkeit des DBVCy-Protokolls (Daunoblastin, Bleomycin, Vincristin, Cytostasan) mit dem ABVD-Protokoll beim fortgeschrittenen Hodgkin-Lymphom. Arch Geschwulstforsch 4: 333–342

Höffken K, Merkle K, Schönfelder M, Anger G, Brandtner M, Ridwelski K, Seeber S (1998) Bendamustine as salvage treatment in patients with advanced progressive breast cancer: a phase II study. J Cancer Res Clin Oncol 124: 627–632

Junghanss C, Heussner P, Krammer-steiner B, Decker S, Petershofen E, Freund M (1996) Ann Hematol 73 [Suppl II]: 536

Jungstand W, Gutsche W, Wohlrab K, Ozegowski W (1971): Wirkung verschiedener Benzimidazol-Losten auf Transplantationstumoren unter besonderer Berücksichtigung von Imet 3393. Zentralbl Pharm Pharmakother Laboratoriumsdiagn 110: 1021–1031

Kahl C, Herold M, Hoffkes HG, Franke A (1997) Bendamustine, methotrexate, mitoxantrone and prednisolone (BMMP) for the treatment of relapsed or refractory high-grade non-Hodgkin's lymphoma. Onkologie 20: 406–408

König U, Junghanss C, Decker S (1999) Response of refractory and relapsed low grade non-Hogkin's lymphoma and chronic lymphocytic leukemia to Dexa-Bid, a bendamustinehydrochlorid containing regimen. Ann Oncol 10: 132

Kramaczyk K, Jungstand W (1971) Vergleichende Untersuchungen zur alkylierenden Reaktivität von Imet 3393 in Blut- und Leberhomogenaten der Maus nach i.v. Applikation. Zentralbl Pharm Pharmakother Laboratoriumsdiagn 110: 1099–1110

Matthias M, Preiss R, Sohr R, Possinger K (1995) Pharmakokinetics of bendamustine in patients with malignant tumors. Proc Am Assoc Clin Oncol 14: 458 (Abstract 1476)

Meyer A, Grischke EM, Wallwiener D, Bastert G (1998) Response and toxicities of chemotherapy with gemcitabine and bendamustine in advanced ovarian and breast cancer. J Cancer Rec Clin Oncol 124: R123 (abstract P1-09.28)

Miller AB, Hoogstraten B, Staquet M, Winkler A (1981) Reporting results of cancer treatment 47: 207–214

Ozegowski W, Krebs D (1971) Gamma(1-Methyl-5-bis(β-chloräthyl)-amino-benzimidazol-(2)) – buttersäure-hydrochlorid, ein neues Zytostatikum aus der Reihe der Benzimidazol-Loste ZBL Pharm 110: 1013–1019

Poenisch W, Mitrou PS, Merkle KM, Rieth A, Herold M, Schulze M, Bittrich A, Assmann M, Schirmer V, Wilhelm G, Dachselt K, Richter P, Subert R, Harksel B, Grobe N, Pillkahn R,

Schulze M, Hoffmann FA, Mittag T, Friedrich T, Helbig W, Niederwieser D (1999) A randomized multicenter study of bendamustine/prednisone versus melphalane/prednisone in the treatment of multiple myeloma. Blood 94: 123a (abstract 542)

Reck M, Haering B, Koschel G, Kaukel E, von Pawel J, Gatzemeier U (1998) Chemotherapie des fortgeschrittenen nicht-kleinzelligen und kleinzelligen Bronchialkarzinoms mit Bendamustin – Eine Phase II-Studie. Pneumologie 52: 571–574

Ruffert K, Jahn H, Syrbe G, Stauch M, Jorke D, Kühne H (1989) Cytostatsan (Bendamustin), in der Alternativtherapie maligner Non-Hodgkin-Lymphome. Z Klin Med 44: 671–74

Ruffert K (1998b) Cytostasan (Bendamustin) in der Therapie maligner Lymphome. In: Fleischer J, Hiddemann W, Hoelzer D (Hrsg) Therapie der Leukämien und Lymphome – Schwerpunkt Zytokine, Bd Karger; Basel, S 256–266

Schadeck-Gressel C, Eberhardt B, Westerhausen M (1998) Bendamustine as immune suppressive agent in five cases of therapy refractory autoimmune thrombocytopenic purpura (ITP). Proc Am Soc Clin Oncol 18: 18a (abstract 65)

Schmidt P, Heck CK, Preiss R (1999) Bendamustine/mitoxantrone in the treatment of advanced breast cancer. Eur J Cancer 35: 324 (abstract 1301)

Schnabel R, Jungstand W, Gutsche W, Grimm H, Fritsch S (1967) Vergleichende Untersuchungen über die zytostatische Wirkung des neuen N-Lost-Derivats "IMET 3393" und Endoxan an drei experimentellen Mäusetumoren (Ehrlich-Karzinom, Sarkom 180 solid, Leukämie LAJ I). Acta Biol Med German 19: 543–558

Schöffski P, Hagedorn T, Grünwald V, Paul H, Merkle, Kowalski, Ganser A (2000) Repeated administration of short infusions of bendamustine: a phase I study in patients with advanced progressive solid tumours. J Cancer Res Clin Oncol 126: 41–47

Schwaenen C, Karakas T, Schrader M (1999) Bendamustine in induction of apoptosis in B-cell chronic lymphocytic leukemia. Ann Oncol 10: 132

Strumberg D, Harstrick A, Doll K, Hoffmann B, Seeber S (1996) Bendamustine hydrochloride activity against doxorubicine-resistant human breast carcinoma cell lines. Anti-Cancer 7: 415–442